



**UNITED STATES ENVIRONMENTAL PROTECTION AGENCY**  
WASHINGTON, D.C. 20460

OFFICE OF  
PREVENTION, PESTICIDES  
AND TOXIC SUBSTANCES

**Note to Reader**  
**January 8, 1998**

**Background:** As part of its effort to involve the public in the implementation of the Food Quality Protection Act of 1996 (FQPA), which is designed to ensure that the United States continues to have the safest and most abundant food supply. EPA is undertaking an effort to open public dockets on the organophosphate pesticides. These dockets will make available to all interested parties documents that were developed as part of the U.S. Environmental Protection Agency's process for making reregistration eligibility decisions and tolerance reassessments consistent with FQPA. The dockets include preliminary health assessments and, where available, ecological risk assessments conducted by EPA, rebuttals or corrections to the risk assessments submitted by chemical registrants, and the Agency's response to the registrants' submissions.

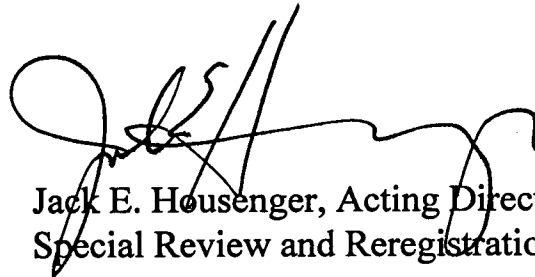
The analyses contained in this docket are preliminary in nature and represent the information available to EPA at the time they were prepared. Additional information may have been submitted to EPA which has not yet been incorporated into these analyses, and registrants or others may be developing relevant information. It's common and appropriate that new information and analyses will be used to revise and refine the evaluations contained in these dockets to make them more comprehensive and realistic. The Agency cautions against premature conclusions based on these preliminary assessments and against any use of information contained in these documents out of their full context. Throughout this process, If unacceptable risks are identified, EPA will act to reduce or eliminate the risks.

There is a 60 day comment period in which the public and all interested parties are invited to submit comments on the information in this docket. Comments should directly relate to this organophosphate and to the information and issues available in the information docket. Once the comment period closes, EPA will review all comments and revise the risk assessments, as necessary.

These preliminary risk assessments represent an early stage in the process by which EPA is evaluating the regulatory requirements applicable to existing pesticides. Through this opportunity for notice and comment, the Agency hopes to advance the openness and scientific soundness underpinning its decisions. This process is designed to assure that America continues to enjoy the safest and most abundant food supply. Through implementation of EPA's tolerance reassessment program under the Food Quality Protection Act, the food supply will become even safer. Leading health experts recommend that all people eat a wide variety of foods, including at least five servings of fruits and vegetables a day.

**Note:** This sheet is provided to help the reader understand how refined and developed the pesticide file is as of the date prepared, what if any changes have occurred recently, and what new information, if any, is expected to be included in the analysis before decisions are made. **It is not meant to be a summary of all current information regarding the chemical.** Rather, the sheet provides some context to better understand the substantive material in the docket ( RED chapters, registrant rebuttals, Agency responses to rebuttals, etc.) for this pesticide.

Further, in some cases, differences may be noted between the RED chapters and the Agency's comprehensive reports on the hazard identification information and safety factors for all organophosphates. In these cases, information in the comprehensive reports is the most current and will, barring the submission of more data that the Agency finds useful, be used in the risk assessments.

A handwritten signature in black ink, appearing to read 'J. Housenger', is written over the typed name and title.

Jack E. Housenger, Acting Director  
Special Review and Reregistration Division

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DATE STAMPED: 07/24/97

MEMORANDUM

SUBJECT: Oxydemeton-Methyl (Metasystox-R™): **Hazard Identification Report (Revised).**

CASRN: 301-12-2  
PC Code: 058702  
Caswell No. 455

From: George Ghali, PhD  
Executive Secretary, Hazard ID Assessment Committee  
Health Effects Division (7509C)

Thru: Karl Baetcke, PhD.  
Acting Chairman, Hazard ID Assessment Committee  
Hazard Identification Division (7509C)

To: William Jacobs, PM 14  
Insecticides-Rodenticides Branch  
Registration Division (7505C)

Pauline Wagner, Chief,  
Reregistration Branch II  
Health Effects Division (7509W)

The Health Effects Division-Hazard Identification Assessment Committee met on July 01 and 02, 1997 to evaluate the existing and/or recently submitted toxicology data in support of oxydemeton-methyl re-registration, and to identify toxicological endpoints and dose levels of concern appropriate for use in risk assessments for different exposure routes and durations. Where no appropriate data have been identified for a particular duration or exposure scenario or if a risk assessment is not warranted, this is noted. Levels of Uncertainties resulting from interspecies extrapolation, intraspecies variability, different routes or variable durations extrapolations are also addressed.

Material available for review consisted of data evaluation records (DERs) for chronic toxicity-carcinogenicity studies in rats (**83-5**), chronic toxicity studies in dogs (**83-1b**), carcinogenicity studies in mice (**83-2b**), reproductive toxicity studies in rats (**83-**

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4), developmental toxicity studies in rats and rabbits (83-3a and -3b), acute and subchronic neurotoxicity studies in rats (81-8 and 82-5b), acute and subchronic delayed neurotoxicity studies in hens (81-7 and 82-5a), subchronic studies in rodents and non-rodent species (82-1a and -1b), non-guideline cholinesterase inhibition studies in human volunteers and in rats, non-guideline sperm motility and fertility studies in rats, and a battery of mutagenicity studies (84-2).

Except for minor revisions, the Committee agreed with the reviewer's evaluation and interpretation of data.

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Individuals in Attendance

Hazard Identification Committee members present were David Anderson, Karl Baetcke (Senior Science Advisor, HED), George Ghali (Executive Secretary, Hazard Identification Committee, HED), Susan Makris, Nancy McCarroll, Kathleen Raffaele, John Redden, and Jess Rowland.

Hazard Identification Committee members in absentia were William Burnam (Chief, SAB, HED), and Clark Swentzel.

Scientific reviewers (Committee or non-committee member(s) responsible for data presentation; signature(s) indicate technical accuracy of panel report).

David Anderson

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I. TOXICOLOGY PROFILE:

A. Chronic and Subchronic Toxicity:

Oxydemeton-methyl is an organophosphorus insecticide. Like all members of this class, the mode of toxic action is the inhibition of cholinesterase.

In a combined chronic toxicity carcinogenicity study, oxydemeton-methyl (50% concentrate in methyl isobutyl ketone) was administered in the diet to Fischer 344 rats at 0.57, 4.6, or 52 ppm (0.027, 0.224 or 3.04 mg/kg/day for males and 0.036, 0.284 or 3.60 mg/kg/day for females) for 118 weeks. The LOEL for brain cholinesterase inhibition was 0.57 ppm (0.027 mg/kg/day in males and 0.036 mg/kg/day in females), the lowest dose tested, based on statistically significant dose-related inhibition of 11% in males and 6% in females at 1-month, and 89% in males and 88% in females at termination. The NOEL/LOEL for plasma and erythrocyte cholinesterase inhibition were 0.57 ppm (0.027 mg/kg/day for males and 0.036 mg/kg/day for females) and 4.6 ppm (0.224 mg/kg/day in males and 0.284 mg/kg/day in females) based on dose-related plasma cholinesterase inhibition of 59% in males and 51% in females; and erythrocyte cholinesterase inhibition of 54% in males and 63% in females at 27 months. (*Hayes, R. (1984), MRID No. 00151806, 40865203, 40865201, 40865202 and 44141301, HED Doc. No. 009544, 005752, 005174, and 012227*).

In another chronic toxicity study, oxydemeton-methyl was administered to 6 Beagle dogs per sex per group by gavage at dose levels of 0, 0.0125, 0.125 or 1.25 mg/kg/day for 12 months. The NOEL/LOEL for plasma cholinesterase inhibition were 0.0125 and 0.125 mg/kg/day, respectively, based on significant inhibition of ≥38% to 48% in males and females at weeks 6 to 52. The NOEL/LOEL for erythrocyte cholinesterase inhibition were 0.0125 and 0.125 mg/kg/day, respectively, in both sexes based on significant inhibition of ≥20% to 25% at week 26 and marginal inhibition of ≥15% to 21% at week 52. The NOEL/LOEL for brain cholinesterase inhibition in females were considered to be 0.125 and 1.25 mg/kg/day, respectively, based on 22% inhibition. The NOEL/LOEL for brain cholinesterase inhibition in males were considered to be 0.0125 and 0.125, respectively, based on 45% inhibition. (*Hoffman, K. and Ruhl, C. (1984). MRID No. 00151805, 41082201, 41980801, 43454201. HED Doc. No. 009544, 005752, 005174, and 012227*).

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B. Subchronic Toxicity:

In a short term study conducted in human volunteers, oxydemeton-methyl (97.5%) in corn oil was administered in capsules to 15 males daily for up to 120 days at dose levels of 0.0125, 0.025, 0.05, 0.25, 0.5, 1.0 or 1.5 mg/kg. One subject was dosed at 0.4 mg/kg/day for 5 days and 1 subject was dosed for 120 days at 0.1 mg/kg/day. Pre-dosing cholinesterase measurements were used as control values. The acute NOEL/LOEL were established at 0.5 and 1.0 mg/kg based on plasma cholinesterase inhibition of 18% and erythrocyte cholinesterase inhibition of 14%. The subacute (30 to 60 day) LOEL was 0.1 mg/kg/day based on one subject showing 40% inhibition of PCHE at 2 weeks and 50% ECHE inhibition at 60 days. The subacute NOEL was 0.05 mg/kg/day based on no effects in 6 subjects at 30 and 60 days (*Doull, J., et al. (Before 1972). MRID No. 00039839, HED Doc. No. 012222*).

In a subacute oral toxicity study, oxydemeton-methyl (94.6%) was administered by gavage in water to 5 Sprague-Dawley rats per sex per group for 14 days at 0, 0.15, 0.45, and 2.5 mg/kg/day. Plasma and erythrocyte cholinesterase activity were monitored at day 0, day 7 and day 14. Brain cholinesterase activity was measured at termination. No cholinergic signs or histopathological changes were observed at any time during the study or at termination. The LOEL for brain cholinesterase inhibition in both males and females was 0.15 mg/kg/day, the lowest dose level tested, based on inhibition of 20% and 12% in males and females, respectively. The NOEL/LOEL for plasma and erythrocyte cholinesterase inhibition in both males and females were 0.15 and 0.45 mg/kg/day, respectively (*Hayes, R. (1987). MRID No. 40499303, HED Doc. No. 012222*).

In a subacute oral toxicity study, oxydemeton-methyl concentrate (50%) was administered in the feed (corn oil and acetone vehicles) to Sprague Dawley rats for 14 days at dietary levels of 3, 9, or 50 ppm (0.22, 0.60, or 3.2 mg/kg/day for males and 0.20, 0.56 or 3.0 mg/kg/day for females). No cholinergic signs were observed. Body weight gain appeared to be reduced in males at the 50 ppm, the highest dose level tested. Brain cholinesterase was significantly inhibited in males and females at all dose levels in a dose-related manner (12-20%, 36-57% and 79-82%). Erythrocyte cholinesterase was consistently inhibited in both sexes at  $\geq 9$  ppm (22-51%). Sporadic statistically significant, but not biologically significant, erythrocyte cholinesterase inhibition was observed in

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both sexes at 3 ppm at week 1 and 2. The LOEL for brain cholinesterase inhibition in both sexes was 3 ppm, the lowest dose level tested. The NOEL/LOEL for erythrocyte cholinesterase inhibition in both sexes were considered to be 3 and 9 ppm, respectively. The NOEL/LOEL for plasma cholinesterase inhibition for both males and females were 3 and 9 ppm, respectively, (*Hayes, R. (1987). MRID No. 40499302, HED Doc. No. 012222*).

In a subacute dermal toxicity study, oxydemeton-methyl (94.6%) was applied as an aqueous solution to 5 Sprague Dawley rats per sex per group, 6 hour per day, for 14 days at 0, 0.3, 1.0, and 5.0 mg/kg/day (MRID# 40499304). Plasma cholinesterase and erythrocyte cholinesterase activity was determined at day 0, 7, and 14. Brain cholinesterase activity was determined at termination. The NOEL/LOEL for erythrocyte and plasma cholinesterase inhibition in both sexes were considered to be 1.0 and 5.0 mg/kg/day, respectively, based on significant ( $p \leq 0.05$ ) erythrocyte cholinesterase inhibition of 26% to 37% in males and 28% to 46% in females; and statistically significant ( $p > 0.05$ ) plasma cholinesterase inhibition of 30% to 38% in males and 40% to 55% in females at week 1 and 2, respectively. The LOEL for brain cholinesterase inhibition in females was 0.3 mg/kg/day, the lowest dose level tested, based on statistically significant ( $p < 0.05$ ) brain cholinesterase inhibition of 11%. The NOEL/LOEL for brain cholinesterase inhibition were 0.3 and 1.0 mg/kg/day, respectively, in males based on inhibition of 12% (*Hayes, R. (1987). MRID No. 40499304, HED Doc. No. 012222*).

In an acute inhalation toxicity study, groups of young adult Sprague Dawley rats were exposed by the inhalation route to oxydemeton-methyl (50% Concentrate, 55.3% a.i. in 50% polyethylene glycol 400 and 50% ethanol) for 4 hours (nose only) at concentrations of 0.177, 0.224, 0.266, 0.370 or 0.540 mg/L. Animals then were observed for 14 days. The  $LC_{50}$  for males was 0.443 mg/L and for females was 0.427 mg/L. The NOEL was  $< 0.177$  mg/L or  $< 0.0979$  mg a.i./L based on clinical signs (tremors) in males and females (note: dose levels should be multiplied by 0.553 to adjust for percent active ingredient).

Dose dependent mortality was seen at  $\geq 0.266$  mg/L in males and females. Death occurred on the day of dosing to day 5 after dosing. Most deaths occurred on day 0 to 2, with only 1 male dying on day 5 and 1 female dying on day 3. Tremors were seen in most

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males and females at all dose levels. In addition, hypoactivity and salivation were seen in most males and females at  $\geq 0.224$  mg/L. Clinical signs ended by day 7. There appeared to be body weight gain decreases in females at  $\geq 0.370$  mg/L and in males at  $\geq 0.224$  mg/L. Single necropsy findings occurred more frequently at  $\geq 0.266$  in males and  $\geq 0.0.370$  mg/L in females, such as salivation, turbinates red, ventrum staining and black zone in the glandular stomach mucosa. No compound related lesions were seen in animals that survived to day 14 (*Shiotsuka, R. 1988, MRID No. 40779805C, 40779805, HED Doc. No. 012197*).

C. Carcinogenicity:

Oxydemeton-methyl did not alter the spontaneous tumor profile in two acceptable carcinogenicity studies in rats (MRID No. **00151806, 40865203, 40865201, 40865202 and 44141301**) and mice (MRID No. 42576601; 00142617, 41038901, 41467401) and was characterized as "**Not likely**" to be a human carcinogen.

D. Reproductive and Developmental Toxicity:

The reproductive/developmental toxicity issues of oxydemeton-methyl were addressed by the HED-Reproductive and Developmental Toxicity Peer Review Committee on September 29, 1992.

1. Reproductive toxicity:

In a reproductive toxicity study, oxydemeton-methyl was administered in the diet to Sprague-Dawley rats at dietary levels of 1, 3, 9, or 50 ppm of 50% ODM, 50 ppm of 94.6% ODM, or 50 ppm of methyl isobutyl ketone (MIBK) (0.043, 0.13, 0.38, 2.1, 2.1, or 0.0 mg/kg/day) Parental systemic toxicity NOEL/LOEL were established at 9 ppm (0.38 mg/kg/day) and 50 ppm (2.1 mg/kg/day) based on decreased male and female fertility of unknown origin in the P and F1 generations, body weight reduction in F1 males and gestating and lactating females of both generations, testes and ovarian weight reduction, decreased number of dams with corpora lutea, and increased estrous cycle length. Parental cholinesterase inhibition LOEL was 1 ppm (0.043 mg/kg/day), the lowest dose level tested, based on brain and RBC cholinesterase inhibition. The offspring NOEL/LOEL were established at 9 ppm (0.38 mg/kg/day) and 50 ppm (2.1 mg/kg/day), respectively, based on decreased litter size at birth and decreased pup weight during lactation. The offspring

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NOEL/LOEL for plasma, RBC and brain cholinesterase inhibition were established at 3 ppm (0.13 mg/kg/day) and 9 ppm (0.38 mg/kg/day) (*Eigenberg, D. (1990). MRID 41461901, HED Doc. No. 012223*).

In another two-generation reproductive toxicity study, oxydemeton methyl (52.5%) in MIBK was administered to Wistar [Bor:WISW(SPF-Cpb)] rats with at dietary levels of 1, 10, or 50 ppm (0.05, 0.5, or 2.5 mg/kg/day; unadjusted for percent purity or for degradation). The parental toxicity NOEL/LOEL were established at 1 and 10 ppm (0.05 and 0.5 mg/kg/day), respectively based on decreased male and female body weight during entire study and reduced gestation body weight for females. Cholinergic signs (slight tremor) were observed at 50 ppm (2.5 mg/kg/day). The reproductive toxicity NOEL/LOEL were 1 ppm and 10 ppm (0.05 and 2.5 mg/kg/day), respectively, based on decreased absolute testis weight, vacuolization of the epithelial cells in the epididymal corpus. The offspring NOEL/LOEL were 1 ppm and 10 ppm (0.05 and 2.5 mg/kg/day), respectively, based on decreased viability index and decreased pup weight during lactation (*Kroetlinger, F. and Kaliner, G. (1985). MRID 00260513, HED Doc. No. 005716*).

In a dominant lethal study with added sperm measures (sperm count, morphology, and motility), and testicular and epididymal histopathology; oxydemeton-methyl was administered by gavage at dose levels of 0.15, 0.9, or 5.0 mg/kg/day for 5 days to male Sprague-Dawley rats, pre mating. The systemic toxicity NOEL/LOEL were 0.9 and 5.0 mg/kg/day based on death, tremors, and body weight decrements. The male reproductive NOEL/LOEL were 0.9 and 5.0 mg/kg/day based on a decrease in epididymal sperm motility, possible decreased numbers of litters produced, possible increased incidence of epididymal vacuolation (*Filler, R. (1989). (MRID 40988001, HED Doc. No. 007494)*).

In a non-guideline study, oxydemeton-methyl was administered at dietary levels of 3, 9, or 50 ppm (0.13, 0.38, or 2.0 mg/kg/day) to male Sprague-Dawley rats for 1, 2, or 3 months. The reproductive toxicity NOEL/LOEL in males were 3 and 9 ppm (0.13 and 2.0 mg/kg/day), respectively, based on an increase in epididymal vacuolation after 2 and 3 months of treatment; no effects on testes weight or sperm motility were observed. The LOEL for cholinesterase inhibition was 3 ppm (0.13 mg/kg/day), the lowest dose level tested, based on decreased brain, erythrocyte, and plasma cholinesterase activity (*Eigenberg, D. (1991). MRID 41834002, HED Doc. No. 012221*).

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In another non-guideline male fertility study, oxydemeton-methyl (92.5%) was administered to male Sprague-Dawley rats at dietary levels of 50 ppm (1.9 mg/kg/day) for 10 weeks. These males were mated with untreated females. The male reproductive toxicity LOEL was 50 ppm (1.9 mg/kg/day), based on a decrease in testes weights, and increased corpus epididymal vacuolation; no effects on fertility were observed. The cholinesterase inhibition LOEL was 50 ppm (1.9 mg/kg/day), based on decreased plasma, brain, and erythrocyte cholinesterase activity at 10 weeks. It was concluded that the fertility effects in the two-generation study are due to effects on the females not the males, and that the epididymal vacuolation probably did not affect male fertility (**Eigenberg, D. and Hastings, . (1992). MRID No. 42499001, 42500101, HED Doc. No. 010117).**

In another non-guideline study conducted to investigate the effect on male fertility, oxydemeton-methyl (54.8%) was administered to Sprague-Dawley rats at dietary levels: 3, 9, or 50 ppm (0.15, 0.45, or 2.5 mg/kg/day) for 1, 2, or 3 months. The reproductive toxicity NOEL/LOEL in males were 3 and 9 ppm (0.15 and 0.45 mg/kg/day, respectively, based on an increase in epididymal vacuolation after 6 and 8 months of treatment. There were equivocal treatment-related changes in sperm count and motility; for rats treated with 50 ppm. The LOEL for erythrocyte and brain cholinesterase inhibition was 3 ppm (0.15 mg/kg/day), the lowest dose level tested. Plasma cholinesterase inhibition was decreased at 50 ppm after 2 months of treatment, at 9 ppm after 4 and 6 months of treatment, and at 3 ppm after 8 months of treatment (**Eigenberg, D. (1987). MRID 40463001, HED Doc. No. 006228, 006596, 012215).**

2. Developmental toxicity:

In a developmental toxicity study, oxydemeton-methyl (90.6%) was administered by gavage to Sprague-Dawley rats at dose levels of 0.5, 1.5, or 4.5 mg/kg/day on GD 6-15. The maternal LOEL was 0.5 mg/kg/day, lowest dose level tested, based on plasma and brain cholinesterase inhibition at GD 16; RBC cholinesterase inhibition was observed at 1.5 mg/kg/day and above; at 4.5 mg/kg/day, maternal body weight values were decreased for GD 6-20, food consumption was decreased on GD 8 and 12, and transient tremors were observed. The developmental toxicity NOEL was  $\geq 4.5$  mg/kg/day, the highest dose level tested (**Clemens, G. et al. (1985). MRID 00146812, 00158342,**

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**HED Doc. No. 012220, 004822, 005585).**

In another developmental toxicity study, oxydemeton-methyl was administered by gavage at dose levels of 0.05, 0.2, or 0.8 mg/kg/day (adjusted for concentration) to American Dutch rabbits on GD 7-19. The maternal NOEL/LOEL were 0.2 and 0.8 mg/kg/day, based on RBC and brain cholinesterase inhibition. The developmental toxicity NOEL was 0.8 mg/kg/day, the highest dose level tested (**Clemens, G. and Hartnagal, R. (1984), MRID 00146989, 00153606, 42859901; HED Doc. No. 003844, 011394, 012220).**

3. Developmental neurotoxicity:

There are no developmental neurotoxicity data on oxydemeton-methyl. No effects of concern were observed in the postnatal segment of the developmental toxicity study in rats. Based upon the weight-of-evidence, the Hazard Identification Assessment Committee did not recommend that a developmental neurotoxicity study in rats be required at this time. This issue should, however, be referred to the Committee on Organophosphorus Pesticides Data Requirements for further consideration.

4. FQPA Considerations:

The data provided no indication of increased sensitivity of rats or rabbits to *in utero* and/or postnatal exposure to oxydemeton-methyl. Therefore, an additional Uncertainty Factor is not warranted.

E. Neurotoxicity:

In an acute delayed neurotoxicity study in hens, a single acute oral dose of 200 mg/kg of oxydemeton-methyl was associated with increased incidence of degeneration (digestion chambers) and axonal swelling at several sites (**Hathway, T. (1984). MRID No. 00146105, 40860001, HED Doc. No. 005174, 012227).**

In a subchronic delayed neurotoxicity study in hens, oxydemeton-methyl was administered at 1, 5, 10 mg/kg/day for 90 days. Although cholinesterase inhibition (whole blood) was seen at all but the lowest dose level, no increase in neuropathology was seen up to and including the highest dose level of 90 mg/kg/day. However, there was some question as to whether a higher dose should

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have been used, given the lack of treatment-related clinical signs at the highest dose (*Sheets, L. (1989). MRID No. 41348201, 43454202, HED Doc. No. 012031*).

In an acute neurotoxicity study in rats, oxydemeton-methyl was administered by gavage at 2.5, 10, or 50 mg/kg to rats. Cholinesterase inhibition (plasma, erythrocyte, and brain) was seen at all dose levels. Although the DER stated the NOEL for neurotoxicity to be 2.5 (with a LOEL of 10), motor activity was significantly decreased in males on day 0 (1.5 hour time point) at the lowest dose (2.5). The data presented in the DER do not allow this effect to be evaluated independently, but the overall NOEL for the study would not be changed, because of the effects on cholinesterase inhibition (*Beyrouty, P. (1995). MRID No. 0000000, HED Doc. No. 012212*).

In a subchronic neurotoxicity study in rats, oxydemeton-methyl was administered in feed at 1 ppm, 10 ppm, or 80 ppm to rats for 90 days. NOEL for neurotoxicity should be at 10 ppm, with LOEL at 80 ppm based on decreased hindlimb grip strength in males and females; decreased motor activity in high dose males at week 4 cannot be evaluated because no statistical information was included in the DER. More information about clinical signs (aggressive behavior, tremors, and fur staining were noted as having occurred) should have been included in the DER. Dose/effect and NOEL could not be determined because of the lack of information. Cholinesterase may have been inhibited at weeks 8 and 13 in plasma for females (percent inhibition was 29% and 21%) (*Beyrouty, P. (1995). MRID No. 0000000, HED Doc. No. 012212*).

F. Mutagenicity:

Twelve acceptable mutagenicity studies were available for review on oxydemeton-methyl (ODM). The following are summaries of the acceptable studies and the committee's conclusions:

a. Gene Mutations:

1) Salmonella typhimurium reverse gene mutation assay (MRID No. 00146091; Doc. Nos. 005174/005752): The test was positive in S. typhimurium TA1535 and TA100 with reproducible and concentration-dependent increases in mutant colonies at 6000-12,000 µg/plate without S9 activation and 3000-12,000 µg/plate with S9 activation.

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2) Mouse lymphoma L5178Y TK<sup>+</sup> forward gene mutation assay (MRID No. 00146102; Doc. No. 005174): The test was positive; dose-related increases in the mutation frequency (MF) were seen at 500-1500 nL/mL without S9 (assumed to be equivalent to ~500-1500 µg/mL) and at 2-50 nL/mL with S9 (~2-50 µg/mL).

3) In vivo mouse spot test (MRID No. 42136901; Document No. 009402): The test was positive for the induction of somatic cell mutations following the intrauterine exposure of embryos to a maternal dose of 20 mg/kg. In this study, C57BL/6J female mice were mated to "T-stock" males and administered single oral gavage doses of 5, 10 or 20 mg/kg ODM (Trial 1) or 12, 16 or 20 mg/kg (Trial 2) on gestation day 10. Deaths (1-5%) and other toxic signs consistent with cholinergic effects were seen at 20 mg/kg; cholinergic effects were also apparent at 16 mg/kg but not at ≤12 mg/kg. The reduction in the number of females bearing live litters seen at the highest dose tested (HDT) parallels the findings from reproduction/fertility studies (see MRID Nos. 41461901, 00260513, 40988001) showing decreased litter size and/or number. In the mutation phase of the study, significant ( $p \leq 0.05$ ) and reproducible increases in mutation were obtained at 20 mg/kg. The data further suggest that the response was dose-related with an ~3.7-fold (but not statistically significant) increase in mutation at 12 mg/kg.

b. Chromosomal Aberrations:

4) In vitro Chinese hamster ovary (CHO) cell chromosome aberration assay (MRID No. 40658502; Doc. No. 007780): The test was positive at 0.5 and 1.0 µL/mL (~500-1000 µg/mL) without S9 activation and at S9-activated doses of 2.5 and 5.0 µL/mL (~2500 and 5000 µg/mL). Severe cytotoxicity and mitotic suppression was noted at higher nonactivated levels.

5) In vitro Chinese hamster ovary (CHO) cell chromosome aberration assay (MRID No. 40534501; Doc. No. 009544): The test was positive; significant and dose-related clastogenic effects were observed at 1000-2000 µg/mL without S9. Significant effects were also noted at 5000 µg/mL with S9 activation. Severe cytotoxicity and mitotic suppression was apparent at higher nonactivated concentrations.

6) In vivo bone marrow cytogenetic assay (MRID Nos. 41236301/41667701; Document Nos. 007881/008973): The assay was negative in male and female Chinese hamsters receiving a single

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oral gavage administration of 40 mg/kg (only dose tested). Toxic signs consistent with cholinesterase inhibition were noted, however, there was no evidence that ODM reached the target tissue.

7) Dominant lethal assay (MRID No. 40628201; Doc. Nos. 006590/006782): Findings were initially considered inconclusive but upon submission of additional data, it was concluded that ODM was negative in CD-1 male mice up to the HDT (4.5 mg/kg administered as a single intraperitoneal injection). Overt toxicity (lethargy and cowering) but no evidence of test material/target cell interaction were recorded at the HDT.

8) Dominant lethal plus assay (MRID No. 40988001; Doc. No. 007494): The test was negative for dominant lethal effects in the germinal cells of male Sprague-Dawley rats administered 0.15-5.0 mg/kg ODM by oral gavage for 5 consecutive days pre-mating. Death and signs of a cholinergic response were reported at the HDT; decreased sperm motility was also seen at 5.0 mg/kg. The Committee noted that effects on sperm motility were not seen in the other dominant lethal assays or in the reproduction, fertility or sperm motility studies examined by the Developmental and Reproductive Peer Review of ODM. Thus, the effects on sperm in this study have not been confirmed.

c. Other Mutagenic Mechanisms:

9) Unscheduled DNA synthesis (UDS) in primary rat hepatocytes (MRID No. 40658503; Doc. No. 007780): The test was negative up to the HDT (1.0  $\mu$ L/mL, equivalent to  $\approx$ 1000  $\mu$ g/mL); higher concentrations ( $\approx$ 2.0  $\mu$ L/mL) were cytotoxic.

10) Sister chromatid exchange (SCE) in CHO cells assay (MRID No. 40658501; Doc. No. 007780): The test was positive with significant increases in SCE induction at all assayed levels (0.08-0.6  $\mu$ L/mL -S9 or 0.6-5  $\mu$ L/mL +S9, equivalent to  $\approx$ 80-600  $\mu$ g/mL -S9 or  $\approx$ 600-5000  $\mu$ g/mL +S9). The response was clearly dose-dependent in the presence of S9 activation and severe mitotic delay occurred at  $\geq$ 0.5  $\mu$ L/mL -S9 ( $\approx$ 500  $\mu$ L/mL).

11) In vitro alkaline elution assay in CHO cells (MRID No. 43776101; Doc. No. 012198): The test was positive; ODM caused reproducible and dose-related increases in DNA single strand breaks at 2000-5000  $\mu$ g/mL -S9 and 500-5000  $\mu$ g/mL +S9.

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12) In vitro alkaline elution assay in primary rat testes cells (MRID No. 43776103; Doc. No. 012198): The test was positive; reproducible and dose-related increases in DNA single strand breaks were noted at 2000-5000 µg/mL -S9; the assay was not performed in the presence of exogenous metabolic activation.

d. Other Information:

In addition to the acceptable data, numerous studies submitted to the Agency were classified as Unacceptable because of a failure to demonstrate the maximum tolerated dose, insufficient primary data or serious technical deficiencies. These studies included: an in vivo alkaline elution assay in rat testes cells, two micronucleus assays, an in vivo SCE assay, two dominant lethal assays, a Bacillus subtilis (H17/M45) rec assay and a reverse gene mutation in Saccharomyces cerevisiae test, a primary rat hepatocyte UDS assay and 13 journal articles. Nevertheless, the Committee concluded that there were sufficient valid data from the acceptable studies to draw meaningful conclusions.

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e. Conclusions (mutagenicity):

Findings from the acceptable genetic toxicology studies indicated that ODM is mutagenic in bacteria and mutagenic and clastogenic in cultured mammalian cells. It also induced mitotic suppression and SCEs in several mammalian cell lines and caused DNA single strand breaks in cultured CHO cells and primary rat testes cells. The results further indicate that ODM is active in vitro in both the presence and absence of S9 activation. The large body of evidence showing that ODM is genotoxic in a wide variety of in vitro test systems submitted by the registrant is also supported by studies in the open literature. ODM was, however, not carcinogenic in chronic rat or mouse feeding studies or clastogenic in the in vivo bone marrow cells of treated Chinese hamsters.

In contrast, Pandita (Mutat. Res. 124:97-102, 1983) reported that the intraperitoneal injection of 10-18 mg/kg ODM once daily for 2 days produced dose-related and significant increases in micronucleated polychromatic erythrocytes recovered from the bone marrow of Swiss albino mice. ODM also induced somatic cell mutations at 20 mg/kg in the in vivo mouse spot test. The data from this study showing that ODM penetrated the placental barrier and caused genetic damage taken in conjunction with the consistent finding of reduced testicular and/or ovarian weights in the reproduction studies and possible adverse effects on sperm motility suggest a potential concern for heritable effects. There is also clear evidence from the in vitro alkaline elution assay that ODM caused DNA single strand breaks in rat testes cells.

The issue as to whether ODM induces DNA single strand breaks in rat testes cells in vivo has, however, not been resolved since the study addressing this endpoint was classified as Unacceptable. Although ODM was negative in the two acceptable in vivo dominant lethal assays, it is not clear whether a potentially genotoxic concentration of ODM was available to interacted with gonadal DNA since the doses used were  $\leq 5$  mg/kg. We based this hypothesis on the data from the metabolism study (see MRID No. 41310201; Doc. No. 008046) in rats showing that low doses of ODM (1 mg/kg) are biotransformed but that biotransformation may be saturated at high doses (20 mg/kg). The results indicating that a marked increased in excretion of the unmetabolized parent (59 or 74% in males or females, respectively) in the urine in conjunction with a marked decline in the excretion of metabolites compared to the corresponding values for males and female rats receiving 1 mg/kg

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(excretion of unmetabolized parent: 34-43% in males and 47-55% in females) strengthens the Committee's position.

Despite the lack of in vivo confirmation of DNA damage in male germinal cells, the Committee concluded that the weight-of-evidence argues for potential adverse heritable effects. Based on the above deliberations, the Committee initially considered requiring a mouse specific locus test since ODM was positive for the indicators of germ cell genotoxicity: in vitro and in vivo mutagenicity, distribution of the test material to the gonads (see MRID No. 41310201; Doc. No. 008046), reduced testicular and/or ovarian weights and decreased size and/or number of litters in the reproduction studies. The Committee, nevertheless, concluded that additional testing to investigate possible genetic damage leading to heritable effects was not warranted at this time. The Committee does recommend, however, that the concern for possible adverse heritable effects be included as an Uncertainty Factor in setting the RfD for ODM.

The Committee concluded that the submitted test battery satisfies the new and pre-1991 mutagenicity initial testing battery guidelines.

G. Dermal Absorption:

Radiolabeled oxydemeton-methyl ( $^{14}\text{C}$ -ODM) was administered dermally or by i.v. injection to 3 Sprague Dawley rats per sex per group per time period at a dose level of about 2 mg/kg by the dermal route or by the i.v. route. Animals were sacrificed 2, 4, 8, 12, 24, 48 and 72 hours and longer when the radioactivity in urine dropped to two times background. For the dermally treated animals, the 12 cm<sup>2</sup> treated skin was removed, washed and counted. Radioactivity was counted from each time period in urine, plasma and the skin, skin solvent wash samples.

The plasma half for the i.v. route was 2 hours for both males and females, and for the dermal treatments was 3 and 4 hours for males and females, respectively and the urine half-life was 5 to 14 hours for males and 2 to 20 hours for females and for the dermal treatments, they were 5 to 10 hours for males and 4 to 9 hours for females. Recoveries were low, probably due to metabolism ( $^{14}\text{CO}_2$  expiration) and failing to include residual total body counts. Total recoveries from i.v. route were 67% for males, 81% for females. Total recoveries from the dermal route were 33% for

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males, 41% for females. 7, 1998 / 058702HA.002

Dermal absorption was calculated to be 50.4% for males and 51.8% for females. The dermal absorption rates as calculated by regression analysis based on mg equivalents of  $^{14}\text{C}$ -ODM over time were  $0.15 \mu\text{g}/\text{cm}^2/\text{hour}$  for males and  $0.17 \mu\text{g}/\text{cm}^2/\text{hour}$  for females (*Bond, G. (1986). MRID No. 001638631, HED Doc. No 005689*).

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II. HAZARD IDENTIFICATION:

Based on comprehensive evaluation of the toxicology data available on oxydemeton-methyl, toxicology endpoints and dose levels of concern have been identified for use in risk assessments corresponding to the categories indicated below. The Committee also determined that these risk assessments are required for oxydemeton-methyl.

A. Reference Dose:

**Reference Dose (RfD):** 0.0005 mg/kg

**NOEL:** 0.05 mg/kg/day, based on inhibition of plasma (18%) and erythrocyte (14%) cholinesterase in human volunteers at 0.1 mg/kg/day.

**Uncertainty Factor (UF):** 100

**Comments:** An Uncertainty Factor (UF) of 10 was applied to account for intraspecies variability. An additional UF of 10 was recommended because of concern regarding: 1) the mutagenic and delayed neurotoxic potential, 2) steep dose response, 3) the study was conducted only in males (females, in some cases, are more sensitive to the effect of cholinesterase inhibitors), and 4) animal data indicated that brain cholinesterase is inhibited in some cases at dose levels below those causing inhibition of plasma and erythrocyte cholinesterase.

**Critical Study:** *Doull, J., et al. (Before 1972). MRID No. 00039839, HED Doc. No. 012222.*

B. Acute Dietary Exposure (one day):

**Dose Level Used in Risk Assessment:** NOEL= 0.05 mg/kg/day based on inhibition of plasma (18%) and erythrocyte (14%) cholinesterase in human volunteers observed at 0.1 mg/kg/day.

**Uncertainty Factor (UF):** An uncertainty factor of 10 was applied to account for intraspecies variability.

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**Comments:** Data from the human study with repeated exposure (30-60 days), and not the single dose exposure, was used for the acute dietary exposure for the following reasons: 1) acute data in the human study was generated based on the evaluation of cholinesterase inhibition in one subject, 2) data from the human study indicated that the inhibition in 30-60 days exposure is not expected to be markedly different from a single exposure, and 3) data from the rat neurotoxicity study indicated that brain cholinesterase was inhibited after a single oral dose.

**Critical Study:** Doull, J., et al. (Before 1972). MRID No. 00039839, HED Doc. No. 012222.

C. Short-Term Occupational or Residential Exposure (1-7 days):

**Dose Level Used for Risk Assessment:** NOEL= 1.0 mg/kg/day based on plasma and erythrocyte cholinesterase inhibition at one week in a 14-day dermal toxicity study in rats at 5.0 mg/kg/day.

**Uncertainty Factor (UF):** An Uncertainty Factor of 100 was applied to account for both interspecies extrapolation and intraspecies variability. An additional Uncertainty Factor of 3 was applied to account for the lack of a NOEL for brain cholinesterase inhibition in females at termination of study at 14 days.

**Critical Study:** Authors..(year). MRID No. 00039839, HED Doc. No. 000000.

D. Intermediate Term Occupational or Residential Exposure:

**Dose Level Used for Risk Assessment:** NOEL= 0.05 mg/kg/day based on plasma (18%) and erythrocyte (14%) cholinesterase inhibition in human volunteers dosed for 30-60 days at 0.1 mg/kg/day.

**Uncertainty Factor (UF):** 100

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**Comments:** Same as acute dietary, see explanation under Section II-A, above. Since the NOEL identified is generated from an oral study, a dermal absorption factor of 50% must be used in risk calculations. When the oral NOEL of 0.05 mg/kg/day is used in conjunction with the 50% dermal absorption rate, the dermal equivalent dose is 0.001 mg/kg/day  $\{[(0.05)/(0.5 \text{ (DA)})]/100 \text{ (UF)}=0.001 \text{ mg/kg/day}\}$ . This dose (0.001 mg/kg/day) is comparable to the dermal dose of 0.003 mg/kg/day used for short-term, using the rat dermal study.

**Critical Study:** Doull, J., et al. (Before 1972). MRID No. 00039839, HED Doc. No. 012222.

E. Chronic Occupational or Residential Exposure:

**Dose Used for Risk Assessment:** NOEL= 0.05 mg/kg/day based on erythrocyte and plasma cholinesterase inhibition in the humans dosed for 30-60 days at 0.1 mg/kg/day.

**Uncertainty Factor (UF):** An Uncertainty Factor of 10 was applied to account for the intraspecies variability, an additional Uncertainty Factor of 10 was applied to account for concerns raised under II.A.

**Comments:** Since the NOEL identified is generated from an oral study, a dermal absorption factor of 50% must be used in risk calculations. When the oral NOEL of 0.05 mg/kg/day is used in conjunction with the 50% dermal absorption rate, the dermal equivalent dose is 0.001 mg/kg/day  $\{[(0.05)/(0.5 \text{ (DA)})]/100 \text{ (UF)}=0.001 \text{ mg/kg/day}\}$ . This dose (0.001 mg/kg/day) is comparable to the dermal dose of 0.003 mg/kg/day used for short-term, using the rat dermal study.

**Critical Study:** Doull, J., et al. (Before 1972). MRID No. 00039839, HED Doc. No. 012222.

F. Inhalation Exposure:

**NOEL:** < 0.177 mg/L or < 0.0979 mg a.i./L based on clinical signs (tremors) in male and female rats.

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Uncertainty Factor (UF): 1000

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**Comments:** A total uncertainty factor (UF) of 1000 was applied; a UF of 100 to account for both interspecies extrapolation and intraspecies variability and an additional UF of 10 was applied to account for the lack of a NOEL in the study. There were no inhalation toxicity studies with longer duration.

**Critical Study:** *Shiotsuka, R. 1988, MRID No. 40779805C, 40779805, HED Doc. No. 012197.*

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